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Deconstructing the Imaginary Worlds of ICER

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Abstract

Despite its manifest flaws and its characterization as pseudoscience (i.e., bunk), the Institute for Clinical and Economic Review (ICER) persists in its production of evidence reviews and the fabrication of imaginary cost-per-quality adjusted life year (QALY) simulacrum. Not to put too fine a point on it, the ICER reference case imaginary world is the antithesis of the scientific method; the process of discovery through conjecture and refutation. This is replaced by a recycling of old assumptions with no thought for hypothesis testing. The focus is on approximate information (proximus notitia). The notion of approximate information is just nonsense. Approximate to some 'unknown' truth; an unknown truth that is specific to each of a multiverse of imaginary worlds? The ICER simulacrum is also flawed in its construction of mathematically illogical QALYs where the utility metric is a manifest score and not a measure that meets the standards of fundamental measurement. Rejecting the ICER modeled imaginary worlds should be standard practice. The recommendations lack any scientific status. To assist health care decision makers in rejecting the ICER model a deconstruction brief is proposed. This brief puts forward a series of questions that should be addressed to ICER or those promoting the ICER evidence report conclusions.

Keywords: imaginary worlds, deconstruction, pseudoscience, nonsense claims, nonsense recommendations

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Introduction

Deconstruction: *the analytic examination of something (such as a theory) often in order to reveal its inadequacy* (Merriam Webster)

One of the more intriguing activities of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) over the past 20 or more years has been the promotion of cost-effectiveness claims based on the construction of imaginary worlds. The key concept is 'approximate information'. Practitioners in health technology assessment, notably in situations where a new therapy has received marketing approval but where data other than those generated by Phase 2 and Phase 3 clinical trials are limited, is the recommendation to create a reference case imaginary world. This recommendation, this support for the technology assessment meme, embedded in practice guidelines, is the reference case frameworks and textbooks has dominated the health technology assessment literature for 30 years. The Institute for Clinical and Economic Review (ICER), a latecomer to this wonderland, has embraced it wholeheartedly. The problem for those advocates of this meme is that it lacks any credibility when judged by the standards of normal science and fails the demarcation test; it is pseudoscience or, in more prosaic terms, bunk.

The purpose of this commentary is to deconstruct the ICER reference case, the blueprint for the construction of imaginary worlds. The inadequacies are manifest; unfortunately all too often media representative and health system decision makers the ICER claims for pharmaceutical pricing and access at face value. They seldom look below the surface, failing to address a series of reasonable questions to determine the scientific status of the many (and ongoing) ICER evidence reports.

The Reference Case Legend

Legend: *a popular myth of recent origin* (Merriam Webster)

The term reference case refers to a set of imaginary modeling standards, established by agencies such as the National Institute for Health and Care Excellence (NICE) in the UK and, as the self-appointed lead technology assessment group in the US, by ICER to create an model simulation extending 10, 20 or 30 years in the future. The purpose of the simulation,

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essentially a fantasy exercise, is to propose an unknown future reality in which the response of a hypothetical population to selected hypothetical therapy interventions can be 'examined'

For a specific disease state with a proposed set of therapy interventions, the reference is designed to generate, within the so-called value assessment framework, claims for comparative benefit expressed in incremental cost-per-QALY terms. Based on a series of assumptions a 'mode' is created that proposes a simulacrum of a future unknown reality, yet known to ICER, where a hypothetical target population is tracked over 10, 20 or 30 years, their therapy response by comparative interventions by stage of disease generating lifetime health related quality of life (HRQoL) and costs. The simulacrum is populated by assumptions generated from the literature, expert advice or just guesswork. QALYs are created for each disease stage by multiplying time spent by utility scores (on a 0 to 1 scale). Aggregating these over the hypothetical lifetime of the patient cohort yields simulated estimates of lifetime QALYs. With fabricated lifetime incremental cost-per-QALY estimates matched against notional willingness to pay thresholds, ICER pronounces on the 'value' of products. If the proposed or assumed WAC price fails to meet the threshold, the ICER recommends pricing discounts and criteria for entry if a notional budget is exceeded.

At the same time, it is of interest to note that a number of manufacturers actually support ICER financially. While no one can object to support for the creation of imaginary worlds, any more than support for fringe evangelical groups, it is odd given manufacturers recognition of the standards of normal science in drug development that they would engage with ICER and its reference case modeling.

The Imaginary Technology Assessment Meme

Imaginary: *existing in the imagination; unreal; illusory* (Free Dictionary)

It is made explicit that it is not the intention in health technology assessment to test hypotheses; rather, to create a model with a lifetime focus for a hypothetical chronic disease population to track, in the modelers imagination (or, at least, that of the software package) response to therapy. The model design precludes any attempt to assess the credibility of claims. It was never intended to. The beauty of the ICER (and ISPOR) meme is that in its applications recommendations can only be challenged by challenging assumptions; that is by developing a 'superior' model.

Commentaries by the present author over the past four years, published in INNOVATIONS in Pharmacy, a University of Minnesota peer-reviewed journal, have made the case that the application of reference case frameworks to support cost-effectiveness claims fail the standards of normal science [1]. They fail the demarcation test between science and pseudoscience; they are seen as intelligent design rather than natural selection [2]. The argument is quite straightforward: since the 17th century and the invention of science (the paradigm shift we call the scientific revolution) the view that science advances through new hypotheses, the testing of hypotheses, the process of 'conjecture and refutation' supporting the discovery of new yet 'provisional' facts has been widely accepted [3]. The cornerstone, the construction of empirically verifiable theories and hypotheses, distinguishes science from pseudoscience (or bunk). This is recognized in drug development and 'set in stone' by agencies such as the FDA and EMA.

Pharmacoeconomics, the purported application of economic concepts to establishing cost-effectiveness claims, rejects the scientific method. Turning its back on normal science, including the standards of mainstream economics in evaluating empirically verifiable theories (positive economics), the meme has to be seen, in retrospect (after some 35 years) as a disaster. Yet a disaster that has yet to be recognized. Why? One obvious explanation is the fact that no group of social scientists want to be confronted by the fact that they have nothing to offer. Building imaginary worlds to support recommendations for pricing and access for pharmaceuticals is, as will be detailed below, 'nonsense on stilts'.

The pharmacoeconomics belief system is readily characterized as a meme; a unit of cultural transmission that supports the proposition that for the believer 'truth is consensus' [4]. Indeed, to characterize a belief system as a sociological phenomenon is appropriate; a shared belief in the construction of fictional imaginary worlds, constructed by assumption, to support non-evaluable claims.

ISPOR is an integral, if not a central element in ensuring the transmission fidelity of the pharmacoeconomic meme [5]. ISPOR ensures the survival of the meme through supporting propagation globally with local chapters, publications, conferences and seminars. There is almost an evangelical intensity to these activities to ensure high copying fidelity while minimizing mutations. Few challenge its 'faith and mysteries' with a continuing supply of recruits for post-graduate training and their placement with pharmaceutical manufacturers and research agencies.

The acceptance of the pharmacoeconomics meme, the belief in its 'faiths and mysteries' is probably best seen in the latest version of the Canadian guideless for technology assessment where is made quite clear that: *economic evaluations are designed to inform decisions. As such they are distinct from conventional research activities which are designed to test*

hypotheses [6]. Apart from questioning what 'informing' means, there is another gem from a 2018 ISPOR Task Force Report: *Leaders in the field of economic evaluation in health care have long recommended that analysts seeking to inform resource allocation decisions approximate the value of interventions in terms of incremental cost-per-QALY gained* [7].

The Mystery of the QALY

Mystery: *Something that is difficult or impossible to understand or explain* (OED)

The QALY, or more precisely, the generic QALY is central to the pharmacoeconomics belief system. A fundamental tenet of the technology assessment meme is that the focus of belief in any pharmacoeconomic evaluation is to determine the incremental cost-effectiveness of the cost per unit of health benefit gained of one unit over another, where the benefit units are QALYs. That is, the time spent in a disease state multiplied by a utility scored on a 0 = death to 1 = perfect health scale. Adding these QALYs over the lifetime of a hypothetical patient cohort yields an estimate of imaginary lifetime QALYs.

It is accepted, without question, that the utility 'values' have ratio measurement properties. That is, there is a true zero which allows arithmetic and statistical operations (e.g., multiplication, estimate of means). The term mystery is appropriate as the evidence points quite clearly to the utility 'values' only having ordinal properties [8] [9]. They are manifest scores which lack even the interval properties of fundamental measurement (i.e., addition, subtraction). The reason is obvious: these utility instruments were not designed to meet standards of fundamental measurement. As detailed in previous commentaries, the notion of Rasch measurement standards eluded those building these instruments; they might meet classical test theory standards but they were not designed to meet Rasch measurement standards [10].

While the purist might argue for rejecting generic QALYs, those subscribing to the pharmacoeconomic belief system have no option. They have to 'assume' that utility scores have the measurement properties required to support their application across the board for any modeled claims, including the creation of 'gold standard' QALYs. If not, the incremental QALY simulacrum collapses; in mathematics it is not logically sustainable.

Of course, there will be a backlash. Challenging a mystery (or a set of mysteries) is not without risks as the early Lutherans found out. The mystery must be respected. This is not an unreasonable position. After all, it is simply one more assumption among the myriad of assumptions gleaned from clinical trials and the literature (or guessed) required to construct what is, after all, merely one of a potential multiverse of competing imaginary worlds. If the followers of the meme concur in this assumption, then truth is consensus.

Belief in Assumptions

Belief: *the feeling of being certain that something exists or is true* (Cambridge Dictionary)

Modeling an imaginary world that may look 10, 20 or 30 years into an unknown yet simulated future is built, by definition, on assumptions selected by the model builder. These may be assumptions regarding the structure of the model or assumptions regarding variables within the model. Belief in the role of assumptions is critical to cost-effectiveness claims.

To the believer in the technology assessment meme, belief in the 'truth' of an assumption (or at least approximate truth) is paramount. Accepting this belief puts to one side Hume's (David Hume 1711-1776) induction problem (even if it is recognized). Plainly stated: no number of singular observations can logically entail and unrestricted general statement. Assumptions cannot be secured. The fact that assumptions have been seen to hold in the past does not mean they will hold in the future. To make assumptions about an unknowable future based on past observations is logically invalid: It cannot be *established by logical argument, since from the fact that all past futures have resembled past pasts, it does not follow that all future futures will resemble future pasts* [11].

The believer, in modeling the future, must put Hume's induction problem to one side; taking refuge, possibly, in different scenarios, sensitivity analyses or even probabilistic claims for the likelihood of non-evaluable modeled outcomes. This is just window dressing. Logical positivism is dead. Hume's induction problem was resolved by Sir Karl Popper (1902-1994) some 80 years ago. We cannot prove the truth of a theory or justify our belief in a theory by attendant assumptions. All we can do is to justify our continued provisional acceptance by ongoing evaluation and replication of claims.

Proximus Notitia

Approximate: ***close to the actual, but not completely accurate or exact*** (OED); ***The truth is out there*** (X-Files)

Apparently, as noted above, the principal role of pharmacoeconomic imaginary modeling is to create 'approximate information' to guide formulary decisions. In contrast, presenting claims for competing products that may, with the appropriate protocol and evidence platform, be evaluated empirically to generate provisional benefit claims is rejected. Pharmacoeconomics dictates the formulation of non-credible claims from lifetime imaginary worlds.

But why should formulary committees accept 'approximate information claims'. Looking up to and beyond 30 years into an unknown future (unless ICER claims its reference case is able to model and predict the winner of the Kentucky Derby in 2030) it is unclear what approximate modeled information over this timeframe means. It certainly fails demarcation criteria to distinguish science from bunk, so the degree of approximation to an unknown 'true' outcome is another mystery. The notion of approximate information, possibly about the Parousia, is a belief, but one that totally lacks, even if it was expected to meet, any standard of scientific credibility. We could equally well talk about approximate disinformation. Yet, for ICER and ISPOR, the truth is 'out there'; the modeled claims are an approximation to that unknown and unknowable truth.

If there is no actual truth, but just one of a multiverse of competing modeled imaginary 'approximate truth' claims, how can we even conceive of being close, but not being completely accurate or exact, in any claim. We cannot approximate to an imaginary point. A point, moreover, which is a moving target within an imaginary undefined space specific to the choice of model construct.

Taking at Face Value

At Face Value: as true or genuine without being questioned or doubted (Merriam Webster)

The response to ICER press releases for the growing number of evidence reports over the past four years makes it quite clear that part of ICER's appeal is that its recommendations, notably for price discounting, are taken by media representative and others at face value. After all, the perennial straw man in health care is pharmaceutical pricing. There are no attempts, apart from the commentaries published in *INNOVATIONS in Pharmacy*, to deconstruct the ICER value assessment framework. Health economics groups at the various pharmaceutical manufacturers seem unable to grasp the obvious limitations to the ICER value assessment methodology, while at the same time supporting ICER financially. Whether this reflects their acceptance of the pharmacoeconomic meme or a more fundamental lack of appreciation of the scientific method and fundamental measurement is an open question. Where criticism is directed it focuses on two aspects of the ICER value framework: (i) on the interpretation of the clinical data and ICER's evaluation of comparative benefit and (ii) on broad and easily deflected complaints that the 'patient voice' is ignored.

The fact that the ISPOR meme, its belief system, faith and mysteries has been embraced by ICER is no defense of what is a ramshackle modeling endeavor. There is no reason to accept pricing and access recommendations based on the ICER imaginary world value assessment framework. At the same time decision makers should not take ICER claims at face value, even if they see them as a bargaining chip in negotiating price discounting and prior authorization barriers.

It is important that ICER claims are challenged by both manufacturers and health system decision makers. This is best achieved by establishing a standard set of questions that, if effected, deconstruct the ICER value assessment model. A similar approach should be taken to any modeled cost-effectiveness claim. An example here would be applications based on the Academy of Managed Care Pharmacy *Format for Formulary Submissions* [12].

Validation of Claims

Validation: *the action of checking or proving the validity or accuracy of something* (Oxford Dictionaries)

Rejection of the scientific method puts to one side any attempt to discover new facts and identify new problems; the process of conjecture and refutation. Rather, ICER validates the approximate claim to an unknown 'truth' (which is not, apparently, even provisional) by an appeal to the 'realism' or 'reasonableness' of the models assumptions. Criteria applied are (i) checking against other imaginary modeled worlds; (ii) testing mathematical functions for consistency; (iii) verifying model calculations; and (iv) varying input parameters with null input values to ensure the model was producing findings consistent with expectations. Welcome to ICER's (and ISPOR's) version of an inductivist world; all our knowledge is based on experience. It's as if Popper had never existed.

Deconstruction Brief: Questions to ICER

Deconstruction: *the analytic examination of something (such as a theory) often in order to reveal its inadequacy* (Merriam-Webster

Manufacturers should be prepared to present an 'ICER Deconstruction Brief' to formulary committees, insurers and other decision makers to challenge acceptance of ICER recommendations. This does not require any engagement with ICER as a stakeholder in the development of a draft and eventually final evidence report. The brief should be available to match media release of ICER final recommendations.

Although engaging as a stakeholder is not recommended, there is no reason why a manufacturer could not present a deconstruction check list as a response to the release of a draft evidence report. If ICER comes to the party, then it would print and respond to the deconstruction questions. These would be in the public domain, potentially forming part of a more comprehensive deconstruction brief. The proposed avenue would be through the public comment process. At the

release of a draft evidence report, ICER asks interested parties to make comments. ICER responds to each of these comments. Prospective questions are detailed in Table 1. These would have to be adapted to the particular circumstances of the draft evidence report: the model, assumptions regarding model structure, choice of utility manifest scores, interpolation of utility scores, time horizon, claims for incremental QALYs, application of threshold values, recommendations for WAC price discounting and access. While the answers to many of these questions are 'known' it is important that ICER states its position. The responses to these questions would be part of the deconstruction brief.

ICER Deconstruction Brief: Structure

The deconstruction brief should not be seen as just an assessment of the potential manifest failings of the modeled cost-effectiveness claims. It needs to cover both the clinical assessment and conclusions that ICER has come to as well as the reference case model. Manufacturers can consider a 'generic' brief as well as the targeting of deconstruction briefs to specific health systems and other decision makers.

The key point is that a deconstruction brief must have educational as well as analytical content. It should not be assumed that the readership is necessarily familiar with the ICER reference framework, the notion of a lifetime 'for approximate information' cost-per-QALY model or, possibly most importantly, the issues of fundamental measurement. Belief in the notion of a 'gold standard' QALY is well entrenched, even among those who are unfamiliar with its structure and the various utility options. Nor should it be assumed that the readership will recognize the limitations of ordinal manifest scores. After all, even those developing, as an example, the EQ-5D-3L (and its putative successor the EQ-5D-5L) were apparently singularly unaware of the importance of fundamental measurement and meeting the standards of Rasch measurement theory in instrument development. This was further complicated by their apparent insistence on a limited health related quality of life measure, completely ignoring the patient voice and the potential for need-fulfillment, disease specific instruments (which would put QALYs to one side).

There are, quite clearly, a number of barriers to overcome, not least of which is the insistence by ISPOR on the contribution of building imaginary worlds. But we have to start somewhere. To be frank, the emphasis on imaginary worlds producing approximate information is, from a normal science perspective, an embarrassment. It is certainly not economics, or at least the mainstream positive economics we have supported for the past century. It is a peculiar outlier. It is almost if the notion of cost-effectiveness demanded a reference case meme. Limited evidence for potential cost-effectiveness at product launch demanded the construction of imaginary worlds to fill a vacuum, to support claims that failed the standards for normal science, claims that were not credible, evaluable and replicable across treatment settings; and an industry was born.

Conclusions

To understand the fundamental flaws in the ICER value assessment framework it is important to ensure that health system decision makers ask the appropriate questions. These should be raised for each evidence report. Taking ICER claims and recommendations at face value must be discouraged. Constructing imaginary incremental cost-per-QALY imaginary worlds may be an easy way of 'establishing' a cost-effectiveness claim, even if we accept that they represent 'approximate information' for an unknown and unknowable 'truth' that, in some sense is 'out there'. This approach is nonsensical. Formulary decisions should be based on real world evidence; not on imaginary world evidence.

Approximate information is indistinguishable from approximate disinformation. If the evidence for cost-effectiveness claims is not present at product launch, then manufacturers should propose how those claims might be assessed in a timeframe appropriate to formulary decisions. Pricing and access can be conditional on the acceptance and application of cost-effectiveness protocols in treatment practice. QALYs are to be rejected unless they are shown to meet the axioms of fundamental measurement. At the same time we should not focus on operational and functional claims for health related quality of life. The patient voice is paramount. This means disease specific instruments that meet required measurement standards and reflect the needs of patients and caregivers. These are not difficult objectives. Unfortunately, there will be ongoing resistance from both ICER, it is their bread and butter business model and ISPOR, defending over 20 years of promoting imaginary worlds. Paradigmatic change is never easy.

TABLE 1

QUESTIONS FOR DECONSTRUCTION: MODELED CLAIMS

1: Choice of Model Framework

1. ***Did ICER undertake a systematic review of the cost-effectiveness models in this disease state for the hypothetical target population?***

   If YES, is this review available?

2. ***Of the possible model options, on what criteria did ICER select the model presented in the final evidence report?***

3. ***Does ICER believe that the model presented represents a 'state of the art' model given standards established by groups such as ISPOR and NICE?***

4. ***Does ICER subscribe to the view that modeled claims should meet the standards of normal science: that they should be credible, evaluable, and replicable?***

   If NOT, why not?

2. Credible Claims

1. ***Does ICER subscribe to the belief that comparative claims for competing pharmaceutical products and devices should be empirically evaluable?***

2. ***Are any of the claims for incremental cost-per-QALY outcomes presented in the final evidence report empirically evaluable?***

   If NOT, why not?

3. ***If YES, are these claims evaluable within a timeframe that can be reported to a formulary committee within 18 months?***

   If NO, why not?

4. ***If a formulary committee requested ICER to produce claims that had the potential for empirical evaluation, would ICER be able to do this?***

   If NO, why not?

   If YES, has ICER proposed a protocol and evidence platform for claims assessment?

3. Utilities

1. ***ICER appears to favor the EQ-5D-3L in creating utilities. Is there any reason why other utility metrics would not be applicable for the value assessment model?***

2. ***Did ICER undertake a systematic review of utility metrics for the target population in this disease state?***

3. ***Does ICER only consider generic utility measures as appropriate for its value assessment modeling?***

4. ***Does the selected generic utility for the target population in the disease state have fundamental measurement (non-ordinal) properties?***

If YES, could ICER demonstrate that the utility measures have properties that are unidimensional, reflecting an underlying latent construct, that meet the axioms of fundamental measurement (invariance of comparisons and sufficiency)?

If YES, could ICER demonstrate that the utility measure meets the standards of Rasch measurement?

4.Quality Adjusted Life Years

1. *If ICER cannot demonstrate that the utility metric has ratio properties, how does ICER justify the creation of QALYs?*
2. *Can ICER provide references to support multiplying time spent in a disease state by a utility manifest score yields a measure (QALY) that can be aggregated over the hypothetical life of a patient across the various stages of a disease?*
3. *Can ICER provide references to support that dividing lifetime modeled discounted hypothetical direct medical costs by discounted lifetime QALYs meet the required standards of fundamental measurement?*
4. *Can ICER provide references to support multiplying time spent in a disease state by a utility manifest score yields a measure (QALY) that can be aggregated over the hypothetical life of a patient across the various stages of a disease?*
5. *Can ICER provide references to support calculating incremental cost per QALY measures when the utility score has only ordinal manifest score properties?*

5.Thresholds

1. *If the utility score has ordinal properties, how does ICER justify applying threshold cost per QALY values to support recommendations for price discounting?*
2. *Why should a formulary committee or other decision makers pay any attention to ICER threshold value assessments when the recommended discount will vary with other modeled imaginary incremental cost be QALY claims?*

6.Approximate Information

1. *Does ICER subscribe to the position taken by ISPOR that reference case modeled claims inform decision makers of the approximate value of interventions in terms of incremental cost-per-QALY gained?*

   If YES, how would ICER define 'approximate' when the modeled construct takes a lifetime perspective, excluding by definition evaluable claims? How is 'approximate information' to be distinguished from 'approximate disinformation'?

   If YES, approximate to what? Does this imply that there is an unknown truth 'out there'? If the truth is 'unknown' how can we talk about 'approximate information'?

   If YES, would alternative reference case modeled constructs to that developed by ICER provide 'approximate information' that is 'closer' to an 'unknown truth'?

   If YES, would ICER apply the same 'approximate information' standard to the presentation and interpretation of clinical data?

   If NO, what is the status of the ICER recommendations?

7.Validation

1. *Does ICER subscribe to the view that to validate a model and the claims generated by that model does not require claims that are credible, evaluable and replicable?*

   If YES, does that mean ICER is not concerned with hypothesis testing for modeled claims?

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